Controlling Nutritional Status (CONUT) Score is a Prognostic Marker in III-IV NSCLC Patients Receiving First-line Chemotherapy

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Research

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Abstract

Background: To investigate the prognostic impact of the controlling nutritional status (CONUT) score in non-small-cell lung cancer (NSCLC) patients receiving first-line chemotherapy.

Methods: We retrospectively reviewed 278 consecutive patients undergoing chemotherapy for stage III-IV NSCLC between May 2012 and July 2020. CONUT score was calculated by incorporating serum albumin, total cholesterol, and total lymphocyte count. The clinicopathological features and follow-up data were evaluated to compare the CONUT score with other prognostic indices, such as the systemic immune-inflammation index (SII) and prognostic nutritional index (PNI), in patients with NSCLC.

Results: Applying cut-offs of ≥ 3 (CONUT), ≥ 443.607 (SII), and ≥ 49.05 (PNI). The high CONUT group had a significantly shorter progression-free survival and overall survival than the low CONUT group. A high CONUT score was significantly associated with older age, worse ECOG PS, advanced clinical stage, and lower PNI (all $P < 0.05$). In the univariate analysis, higher SII, higher CONUT, advanced clinical stage and lower PNI were associated with worse PFS ($P < 0.05$). Worse ECOG PS, higher SII, higher CONUT, advanced clinical stage and lower PNI were associated with worse OS ($P < 0.05$). In multivariate analysis, SII and CONUT score were independently correlated with PFS ($P < 0.05$), while PNI and CONUT score were independently correlated with OS ($P < 0.05$).

Conclusion: CONUT score is an independent prognostic indicator of poor outcomes for patients with stage III-IV NSCLC and is superior to the SII and PNI in terms of prognostic ability.

Trial registration: retrospectively registered.

Background

Non-small-cell lung cancer (NSCLC) is the most common cause of cancer-related death and a major public health problem worldwide, accounting for more than one million deaths annually.[1, 2] Over the last 20 years, the treatment strategies for advanced and metastatic NSCLC have dramatically changed. Although the treatments in lung cancer have made great progress,[3] more effective treatment strategies must consider patient selection and evaluate the prognosis of patients with NSCLC. Recently, there has been increasing interest in identifying prognostic factors for tailored treatment.

Recently, patient immunonutritional status has been linked to treatment outcome. Immunonutritional status is an important feature of the tumour microenvironment and is associated with poor prognosis of various types of tumours. [4, 5] Prognostic nutritional index (PNI) is a proven scoring system based on immunonutritional status that allows an estimation of treatment tolerability and cancer progression.[6] Inflammation is also reported to be associated with cancer prognosis. Haematological inflammatory parameters such as neutrophils, lymphocytes, monocytes, and platelets can reflect systemic and focal inflammation and have important value in predicting the prognosis of tumours, including NSCLC.[7, 8]

The Controlling Nutritional Status (CONUT) score is a new scoring system for patient immunonutritional status that has attracted substantial attention and is reported to be associated with clinical outcomes in various malignancies. Similar to the PNI and systematic inflammation index (SII),[9, 10] the CONUT score is easily obtained and calculated from three clinical parameters: serum albumin, total cholesterol, and total lymphocyte count.[11] It has been reported that the CONUT score can be a predictive or prognostic marker in many types of cancers. For NSCLC, some reports have shown that the CONUT score is useful for predicting long-term outcomes of surgery and immune therapy. [12-

14] However, few studies have reported whether the CONUT score is associated with the prognosis of NSCLC patients treated with chemotherapy.

The aim of this retrospective study was to determine whether prechemotherapy CONUT score could be a useful predictor of survival in patients with NSCLC and to compare the accuracy of the CONUT score, PNI and SII as predictors of the survival rate of such patients.

Materials And Methods

Patients

We retrospectively enrolled 278 patients diagnosed with advanced NSCLC who regularly received DP (docetaxel plus cisplatin), GP (gemcitabine plus cisplatin), NP (vinorelbine plus cisplatin), PC (pemetrexed plus cisplatin) and TP (paclitaxel plus cisplatin) chemotherapy regimens at the Affiliated Hospital of Xu Zhou Medical University from January May 2012 and July 2020.

The inclusion criteria were as follows:

(1) NSCLC was pathologically diagnosed; (2) NSCLC was stage III or IV according to the American Joint Committee on Cancer (AJCC) 8th edition; (3) the patient received chemotherapy for more than two cycles without a combination of targeted therapy, radiation therapy and immune therapy; (4) the patient had no other cancer history and laboratory test results were obtained before treatment.

The exclusion criteria were as follows: (1) patients with missing or incomplete data; (2) patients who underwent surgery, radiotherapy, immunotherapy before standard chemotherapy protocols, (3) patients who had obvious fever and pneumonia before chemotherapy.

This retrospective study was approved by the ethics committee of the Affiliated Hospital of Xu Zhou Medical University.

Data collection and follow-up

Data, including age, sex, histological subtype, stage, smoking status, chemotherapy regime, Eastern Cooperative Oncology Group Performance Status (ECOG PS) scores, routine blood parameters and biochemical profiles, were collected retrospectively from individual medical case notes, electronic patient records and pathology reports. Blood samples were obtained and assayed within 2 weeks before chemotherapy. CONUT scores were summarized using the serum albumin concentration, peripheral lymphocyte counts and the total cholesterol concentration, as described in Table 1. The following formula was used to calculate PNI and SII. PNI: albumin (g/L) × total lymphocyte count × 10⁹/L. SII: platelet count × neutrophil count/lymphocyte count. [9, 15]

Follow-up was performed every 3 months. All patients were monitored either until July 2020 or until death. The median follow-up time was 24 months (range, 3–75 months). PFS was defined as the interval from treatment initiation until disease progression or death. OS was defined as the interval from treatment initiation until the date of death or the date of last follow-up for patients who had not died before the censor date.

Table 1. The CONUT scoring system.

Parameters	Normal	Light	Moderate	Severe
Serum albumin (g/dL)	≥ 3.5	3.0-3.4	2.5-2.9	≤ 2.5
score	0	2	4	6
Total lymphocyte count/mm ³	≥ 1600	1200-1599	800-1199	≤ 800
score	0	1	2	3
Total cholesterol (mg/dl)	≥ 180	140-179	100-139	≤ 100
score	0	1	2	3
CONUT score (total)	0-1	2-4	5-8	9-12

Statistical analysis

The associations between CONUT score and clinicopathological characteristics were analysed using χ^2 tests. The patients were classified into two groups based on receiver operating characteristic (ROC) curves. To evaluate whether the CONUT score, PNI and SII have value for prognosis, we used ROC curves. Survival analysis was performed using Kaplan–Meier method. The differences between the survival curves were compared by log-rank test. Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). A P value <0.05 was considered to indicate statistical significance. The results were analysed using SPSS 21.0.

Results

ROC analysis

ROC analysis was performed to identify the optimal cut-off point with the highest sensitivity and specificity, which was 443.607 for SII, 49.05 for PNI, and 3 for CONUT (sensitivity and specificity: 0.414 and 0.750 for SII, 0.425 and 0.708 for PNI, and 0.857 and 0.524 for CONUT, respectively). For each index, patients were divided into two groups for further analysis [SII <443.607 (low) and SII $\geq$ 443.607 (high); PNI <49.05 (low) and PNI $\geq$ 49.05 (high); CONUT < 3 (low) and CONUT $\geq$ 3 (high)]. The AUCs of the SII, PNI, and CONUT for OS were 0.602, 0.566, and 0.707, respectively (Figure 1a), and the AUC values for OS were 0.597, 0.558, and 0.701, respectively (Figure 1b). Hence, among the three indices analysed in the present study, CONUT was the best predictor of long-term survival in cases with NSCLC.

CONUT, controlling nutritional status; SII, systemic immune-inflammation index; PNI, prognostic nutritional index;

Baseline characteristics of patients

In total, 278 cases were enrolled in the present study, of which 192 (69.1%) patients were male, 162 (58.3%) patients had a smoking history, and 176 (63.3%) patients had stage IV disease. A total of 114 (41.1%) patients were classified into the high CONUT group, and 164 (59.0%) patients were classified into the low CONUT group based on the cut-off value of 3. A total of 257 (92.4%) patients were divided into the high SII group, and 21 (7.6%) were divided into the low SII group based on the cut-off value of 443.607. A total of 127 (45.7%) patients were stratified into the high PNI group, and 151 (54.3%) were stratified into the low PNI group based on the cut-off value of 49.05. The

characteristics of all patients are detailed in Table 2. A high CONUT score was significantly associated with older age, worse ECOG PS, advanced clinical stage, and lower PNI (all $P < 0.05$)

Prognostic value of SII, PNI, and CONUT

In the present study, we found that CONUT≤3 before treatment was associated with longer PFS and OS (Figure 2). After stratification by TNM stage, the prognostic significance of the CONUT score was also maintained in patients with stage III and stage IV disease. (Figure 3)

A univariate analysis of the factors associated with PFS indicated that higher SII, higher CONUT, advanced clinical stage and lower PNI were factors associated with worse survival (Table 3). A multivariate analysis indicated that SII and CONUT were significant independent prognostic parameters for PFS (Table 4).

Table 2. The relationship between CONUT score and clinicopathological characteristics of the patients [*n* (%)].

Variable	Total	CONUT score		χ^2	P
		<3 [n=164]	≥3 [n=114]		
Gender				0.742	0.389
Male	192(69.1)	110(67.1)	82(71.9)		
Female	86(30.9)	54(32.9)	32(28.1)		
Age				8.537	0.003
<60	109(39.2)	76(46.3)	33(28.9)		
≥60	169(60.8)	88(53.7)	81(71.1)		
Smoking status				1.276	0.259
Minimal/never	116(41.7)	73(44.5)	43(37.7)		
Current/former	162(58.3)	91(55.5)	71(62.3)		
ECOG-PS				5.623	0.018
0/1	160(57.6)	104(63.4)	56(49.1)		
2	118(42.4)	60(36.6)	58(50.9)		
Histology subtype				3.272	0.195
Squamous	113(40.6)	60(36.6)	53(46.5)		
Adenocarcinoma	133(47.8)	82(50.0)	51(44.7)		
others	32(11.5)	22(13.4)	10(8.8)		
TNM staging				7.504	0.006
III	102(36.7)	71(43.3)	31(27.2)		
IV	176(63.3)	93(56.7)	83(72.8)		
Chemotherapy regimens				5.691	0.233
DP	32(11.5)	17(10.4)	15(13.2)		
GP	97(34.9)	55(33.5)	42(36.8)		
NP	37(13.3)	23(14.0)	14(12.3)		
PC	83(29.9)	56(34.1)	27(23.7)		
TP	29(10.4)	13(7.9)	16(14.0)		
Metastasis				5.122	0.077
0	103(37.1)	53(32.3)	50(43.9)		
1	122(43.9)	74(45.1)	48(42.1)		
2+	53(19.1)	37(22.6)	16(14.0)		
CEA				0.764	0.382

Normal	123(44.2)	69(42.1)	54(47.4)		
High	155(55.8)	95(57.9)	60(52.6)		
CYF				0.750	0.386
Normal	76(27.3)	48(29.3)	28(24.6)		
High	202(72.7)	116(70.7)	86(75.4)		
NSE				0.638	0.424
Normal	153(55.0)	87(53.0)	66(57.9)		
High	125(45.0)	77(47.0)	48(42.1)		
SII				2.777	0.096
<443.607	21(7.6)	16(9.8)	5(4.4)		
≥443.607	257(92.4)	148(90.2)	109(95.6)		
PNI				54.217	<0.001
≥49.05	127(45.7)	105(64.0)	22(19.3)		
<49.05	151(54.3)	59(36.0)	92(80.7)		

ECOG-PS, Eastern Cooperative Oncology Group performance status; TNM, tumor-node-metastasis; CONUT, controlling nutritional status; SII, systemic immune-inflammation index; PNI, prognostic nutritional index; DP, docetaxel plus cisplatin; GP, gemcitabine plus cisplatin; NP, vinorelbine plus cisplatin; PC, pemetrexed plus cisplatin; TP, paclitaxel plus cisplatin.

Table 3. Univariate analysis of potential factors associated with PFS and OS [Median (Q25, Q75)].

Variable	Total	PFS	χ^2	<i>P</i>	OS	χ^2	<i>P</i>
Gender			0.769	0.381		2.584	0.108
Male	192(69.1)	6.0(5.16,6.85)			25.0(22.25,27.75)		
Female	86(30.9)	6.0(4.18,7.82)			26.00(20.88,31.12)		
Age			0.899	0.343		1.881	0.170
<60	109(39.2)	6.0(5.28,6.72)			26.0(22.96,29.05)		
≥60	169(60.8)	6.0(4.84,7.16)			23.0(19.26,26.74)		
Smoking status			0.065	0.799		1.598	0.206
Minimal/never	116(41.7)	6.0(4.76,7.24)			25.0(20.25,29.75)		
Current/former	162(58.3)	6.0(4.96,7.04)			25.0(22.16,27.84)		
ECOG-PS			1.615	0.204		5.642	0.018
0/1	160(57.6)	6.0(4.97,7.03)			27.0(24.68,29.32)		
2	118(42.4)	6.0(4.94,7.06)			22.0(19.76,24.24)		
Histology subtype			0.646	0.724		1.730	0.421
Squamous	113(40.6)	6.0(4.85,7.15)			25.0(22.48,27.52)		
Adenocarcinoma	133(47.8)	6.0(4.67,7.33)			25.0(20.72,29.28)		
others	32(11.5)	6.0(4.63,7.38)			26.0(15.7,36.26)		
TNM staging			6.549	0.010		12.981	<0.001
III	102(36.7)	6.0(5.24,6.76)			27.0(23.35,30.65)		
IV	176(63.3)	6.0(4.76,7.24)			23.0(20.23,25.77)		
Chemotherapy regimens			1.156	0.885		1.419	0.841
DP	32(11.5)	5.0(1.67,8.33)			20.0(14.46,25.54)		
GP	97(34.9)	6.0(4.79,7.21)			26.0(22.08,29.92)		
NP	37(13.3)	7.0(4.02,9.98)			23.0(15.87,30.13)		
PC	83(29.9)	6.0(5.01,6.99)			25.0(20.71,29.29)		
TP	29(10.4)	5.0(3.49,6.51)			26.0(19.87,32.13)		
Metastasis			1.424	0.491		3.373	0.185
0	103(37.1)	6.0(5.06,6.94)			23.0(19.74,26.27)		
1	122(43.9)	6.0(4.59,7.41)			26.0(22.93,29.07)		

2+	53(19.1)	6.0(3.97,8.04)			27.0(18.05,35.95)	
CEA			3.240	0.072		2.163 0.141
Normal	123(44.2)	6.0(5.06,6.94)			25.0(22.02,27.98)	
High	155(55.8)	6.0(4.54,7.46)			26.0(22.39,29.61)	
CYF			3.147	0.076		1.105 0.293
Normal	76(27.3)	6.0(4.88,7.13)			25.0(21.92,28.08)	
High	202(72.7)	6.0(4.97,7.03)			25.0(22.08,27.93)	
NSE			0.945	0.331		1.406 0.236
Normal	153(55.0)	6.0(4.99,7.01)			23.0(20.49,25.51)	
High	125(45.0)	6.0(4.71,7.29)			26.0(22.07,29.93)	
SII			11.779	0.001		7.963 0.005
<443.607	21(7.6)	15(6.97,23.03)			40.0(29.18,50.82)	
≥443.607	257(92.4)	6.0(5.42,6.58)			23.0(20.86,25.14)	
PNI			12.750	<0.001		46.426 <0.001
≥49.05	127(45.7)	7.0(5.82,8.18)			31.0(27.72,34.28)	
<49.05	151(54.3)	5.0(4.14,5.86)			18.0(15.50,20.51)	
CONUT score			62.912	<0.001		78.963 <0.001
<3	164(59.0)	8.0(5.72,10.28)			30.0(27.58,32.42)	
≥3	114(41.1)	4.0(3.13,4.87)			16.0(14.17,17.83)	

ECOG-PS, Eastern Cooperative Oncology Group performance status; TNM, tumor-node-metastasis; CONUT, controlling nutritional status; SII, systemic immune-inflammation index; PNI, prognostic nutritional index; DP, docetaxel plus cisplatin; GP, gemcitabine plus cisplatin; NP, vinorelbine plus cisplatin; PC, pemetrexed plus cisplatin; TP, paclitaxel plus cisplatin.

In Cox hazard analyses, univariate analysis showed that ECOG PS, SII, CONUT score, clinical stage and PNI were significantly associated with OS (Table 3). After the exclusion of variables that showed no impact on OS in univariate analysis, Cox multivariate regression analysis was performed, which identified only PNI and CONUT score as independent prognostic factors of OS (Table 4).

Table 4. Multivariable Cox regression analyses for PFS and OS.

Variable	PFS			OS		
	<i>HR(95% CI)</i>	<i>Waldχ^2</i>	<i>P</i>	<i>HR(95% CI)</i>	<i>Waldχ^2</i>	<i>P</i>
SII	2.108(1.242~3.578)	7.628	0.006	1.760(0.979~3.165)	3.566	0.059
PNI	0.996(0.751~1.32)	0.001	0.976	1.529(1.128~2.073)	7.489	0.006
CONUT score	2.524(1.864~3.417)	35.882	0.000	2.305(1.689~3.145)	27.741	0.000
ECOG-PS	-	-	-	1.002(0.771~1.303)	0.001	0.987
TNM staging	1.15(0.875~1.512)	1.003	0.317	1.182(0.875~1.596)	1.185	0.276

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; SII, systemic immune inflammation index; PNI, prognostic nutritional index; ECOG-PS, Eastern Cooperative Oncology Group performance status; CONUT, controlling nutritional status; TNM, tumor-node-metastasis;

Discussion

In the present study, we established an immune-nutrition-based prognostic index (CONUT) based on serum albumin, total cholesterol, and total lymphocyte count and demonstrated the prognostic value of CONUT in III-IV NSCLC. To our knowledge, this is the first report investigating the prognostic value of CONUT and comparing the superiority between nutrition-based indices and inflammation-based indices in patients with advanced NSCLC treated with chemotherapy. Moreover, the results indicated that CONUT score was associated with age, ECOG PS, clinical stage, and PNI. Significantly, without considering the tumour stage, CONUT independently predicted the prognosis of NSCLC patients. Compared with low CONUT scores, high CONUT scores predicted shorter PFS and OS.

As mentioned above, the prognostic nutritional index (PNI), as a nutrition-based index, which was calculated from the serum albumin concentration and the total peripheral lymphocyte count, has been reported to correlate with survival in NSCLC patients.[16] It is not difficult to see that the two indices of PNI are covered by the CONUT scoring system. The serum albumin concentration is a common nutritional status indicator that can be influenced by many other factors, such as liver function, inflammation, infection, dehydration and so on.[17, 18] Hence, to reduce the weight of serum albumin, some scholars proposed adding plasma cholesterol levels to optimize the PNI scoring system.[19]. In addition, cytokines and CRP also modulate the production of albumin.[17, 18] As cholesterol plays a crucial role in influencing cell membrane fluidity, cholesterol affects the mobility of cell surface receptors and their ability to transmit signals. Moreover, serum cholesterol levels influence caloric intake.[19] Lymphocytes play a key role in initiating cellular immunity, and high numbers of infiltrating lymphocytes are associated with good prognosis. [20, 21] Therefore, the combination of these three parameters could balance the impact of each parameter.

Inflammation-based indices also act as oncological prognosis biomarkers. A series of inflammation indices, such as NLR, PLR, LMR and SII, showed positive correlations with poor survival outcome in patients with lung cancer[18, 22, 23]. Some reports have also illuminated that the SII is a superior prognostic factor for survival outcome compared to the NLR and PLR[24]; therefore, we selected the SII as the representative inflammation prognostic index. It is not hard to see that serum albumin and cholesterol are not only nutrition indices but also inflammatory indices. However, the SII is a pure inflammatory index based on neutrophils, lymphocytes, and platelets and is more easily affected by external factors, such as pneumonia. Furthermore, separate analyses of the prognostic value of the SII in patients with stage III NSCLC showed no significant effects on either PFS or OS, which, from another perspective,

illustrates that the CONUT score is superior to the SII (p all >0.05 , data not shown). Therefore, we hypothesize that CONUT is a superior prognostic biomarker that not only reflects the features of tumour cells but also reflects the nutritional status of patients.

The present study has certain limitations. First, this is a retrospective analysis; hence, there are several potential factors that might have influenced the studied results, such as lipid-lowering agents. Second, data for all patients were collected from a single institute, and the number of patients was relatively small. Third, different nutritional support in the process of chemotherapy might have confounded our results. Therefore, a multi-institutional investigation, especially a prospective validation study, is needed to confirm the results.

Conclusion

The present study indicates that CONUT is an independent prognostic indicator of poor outcomes for patients with stage III-IV NSCLC and is superior to SII and PNI in terms of prognostic ability.

List Of Abbreviations

ECOG-PS, Eastern Cooperative Oncology Group performance status; TNM, tumor-node-metastasis; CONUT, controlling nutritional status; SII, systemic immune-inflammation index; PNI, prognostic nutritional index; DP, docetaxel plus cisplatin; GP, gemcitabine plus cisplatin; NP, vinorelbine plus cisplatin; PC, pemetrexed plus cisplatin; TP, paclitaxel plus cisplatin. HR, hazard ratio; 95% CI, 95% confidence interval

Declarations

Ethical approval

For this type of study, formal consent is not required.

Consent for publication

We declare that the manuscript, including related data, figures and tables has not been published previously and that the manuscript is not under consideration elsewhere.

Availability of data and materials

All data included in the present study were presented in the main manuscript

Competing interests

The authors have stated that they have no conflicts of interest.

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Authors' contributions

YZ and ZQZ conceived and designed the experiments and were responsible for data analysis and writing the manuscript. FFK were responsible for providing the clinical samples. FFK and YZ was responsible for data

collection. All authors read and approved the final manuscript.

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References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, Znaor A, Bray F: Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 2019, 144:1941-1953
2. Torre LA, Siegel RL, Jemal A: Lung Cancer Statistics. *Adv Exp Med Biol* 2016, 893:1-19.
3. Cortot AB, Audigier-Valette C, Molinier O, Le Moulec S, Barlesi F, Zalcman G, Dumont P, Pouessel D, Poulet C, Fontaine-Delaruelle C, et al: Weekly paclitaxel plus bevacizumab versus docetaxel as second- or third-line treatment in advanced non-squamous non-small-cell lung cancer: Results of the IFCT-1103 ULTIMATE study. *Eur J Cancer* 2020, 131:27-36.
4. Li W, Li M, Wang T, Ma G, Deng Y, Pu D, Liu Z, Wu Q, Liu X, Zhou Q: Controlling Nutritional Status (CONUT) score is a prognostic factor in patients with resected breast cancer. *Sci Rep* 2020, 10:6633.
5. Daitoku N, Miyamoto Y, Tokunaga R, Sakamoto Y, Hiyoshi Y, Iwatsuki M, Baba Y, Iwagami S, Yoshida N, Baba H: Controlling Nutritional Status (CONUT) Score Is a Prognostic Marker in Metastatic Colorectal Cancer Patients Receiving First-line Chemotherapy. *Anticancer Res* 2018, 38:4883-4888.
6. Shoji F, Morodomi Y, Akamine T, Takamori S, Katsura M, Takada K, Suzuki Y, Fujishita T, Okamoto T, Maehara Y: Predictive impact for postoperative recurrence using the preoperative prognostic nutritional index in pathological stage I non-small cell lung cancer. *Lung Cancer* 2016, 98:15-21.
7. Scilla KA, Bentzen SM, Lam VK, Mohindra P, Nichols EM, Vyfhuis MA, Bhooshan N, Feigenberg SJ, Edelman MJ, Feliciano JL: Neutrophil-Lymphocyte Ratio Is a Prognostic Marker in Patients with Locally Advanced (Stage IIIA and IIIB) Non-Small Cell Lung Cancer Treated with Combined Modality Therapy. *Oncologist* 2017, 22:737-742.
8. Mandaliya H, Jones M, Oldmeadow C, Nordman, II: Prognostic biomarkers in stage IV non-small cell lung cancer (NSCLC): neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR), platelet to lymphocyte ratio (PLR) and advanced lung cancer inflammation index (ALI). *Transl Lung Cancer Res* 2019, 8:886-894.
9. Hu Y, Shen J, Liu R, Feng Z, Zhang C, Ling L, Chen L: Prognostic value of pretreatment prognostic nutritional index in non-small cell lung cancer: A systematic review and meta-analysis. *The International Journal of Biological Markers* 2018, 33:372-378.
10. Fest J, Ruiter R, Mulder M, Groot Koerkamp B, Ikram MA, Stricker BH, van Eijck CHJ: The systemic immune-inflammation index is associated with an increased risk of incident cancer-A population-based cohort study. *Int J Cancer* 2020, 146:692-698.

11. Liu X, Zhang D, Lin E, Chen Y, Li W, Chen Y, Sun X, Zhou Z: Preoperative controlling nutritional status (CONUT) score as a predictor of long-term outcome after curative resection followed by adjuvant chemotherapy in stage II-III gastric Cancer. *BMC Cancer* 2018, 18:699.
12. Shoji F, Haratake N, Akamine T, Takamori S, Katsura M, Takada K, Toyokawa G, Okamoto T, Maehara Y: The Preoperative Controlling Nutritional Status Score Predicts Survival After Curative Surgery in Patients with Pathological Stage I Non-small Cell Lung Cancer. *Anticancer Res* 2017, 37:741-747.
13. Toyokawa G, Kozuma Y, Matsubara T, Haratake N, Takamori S, Akamine T, Takada K, Katsura M, Shimokawa M, Shoji F, et al: Prognostic impact of controlling nutritional status score in resected lung squamous cell carcinoma. *J Thorac Dis* 2017, 9:2942-2951.
14. Ohba T, Takamori S, Toyozawa R, Nosaki K, Umeyama Y, Haratake N, Miura N, Yamaguchi M, Taguchi K, Seto T, et al: Prognostic impact of the Controlling Nutritional Status score in patients with non-small cell lung cancer treated with pembrolizumab. *J Thorac Dis* 2019, 11:3757-3768.
15. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, Zhang X, Wang WM, Qiu SJ, Zhou J, Fan J: Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. *Clin Cancer Res* 2014, 20:6212-6222.
16. Ozdemir Y, Topkan E, Mertsoylu H, Selek U: Low Prognostic Nutritional Index Predicts Poor Clinical Outcomes in Patients with Stage IIIB Non-small-cell Lung Carcinoma Undergoing Chemoradiotherapy. *Cancer Manag Res* 2020, 12:1959-1967.
17. Ignacio de Ulíbarri J, González-Madroño A, de Villar NG, González P, González B, Mancha A, et al: CONUT: a tool for controlling nutritional status. First validation in a hospital population. *Nutr Hosp.* 2005 Jan-Feb;20:38-45..
18. de Ulíbarri Perez JI, Fernandez G, Rodriguez Salvanes F, Diaz Lopez AM: Nutritional screening; control of clinical undernutrition with analytical parameters. *Nutr Hosp* 2014, 29:797-811.
19. Sun KY, Xu JB, Chen SL, Yuan YJ, Wu H, Peng JJ, Chen CQ, Guo P, Hao YT, He YL: Novel immunological and nutritional-based prognostic index for gastric cancer. *World J Gastroenterol* 2015, 21:5961-5971.
20. Cengiz O, Kocer B, Surmeli S, Santicky MJ, Soran A: Are pretreatment serum albumin and cholesterol levels prognostic tools in patients with colorectal carcinoma? *Med Sci Monit* 2006, 12:CR240-247.
21. Heys SD, Walker LG, Deehan DJ, Eremin OE: Serum albumin: a prognostic indicator in patients with colorectal cancer. *J R Coll Surg Edinb* 1998, 43:163-168.
22. Lee H, Jeong C, Kwak C, Kim H, Seo S, Lee H, Oh J, Lee S, Hong S, Lee S, Byun S: Preoperative Cholesterol Level Is Associated With Worse Pathological Outcomes and Postoperative Survival in Localized Renal Cell Carcinoma Patients: A Propensity Score-Matched Study. *Clin Genitourin Cancer* 2017, 15:e935-e941.
23. Lee SH, Lee JY, Hong TH, Kim BO, Lee YJ, Lee JG: Severe persistent hypocholesterolemia after emergency gastrointestinal surgery predicts in-hospital mortality in critically ill patients with diffuse peritonitis. *PLoS One* 2018, 13:e0200187.
24. Chen JH, Zhai ET, Yuan YJ, Wu KM, Xu JB, Peng JJ, et al: Systemic immune-inflammation index for predicting prognosis of colorectal cancer. *World J Gastroenterol.* 2017 Sep 14;23:6261-6272.

Figures

Figure 1

The ROC curves of CONUT, SII and PNI for predicting PFS (a) and OS (b).

Figure 2

Kaplan-Meier survival analyses of the correlation between CONUT and survival among NSCLC patients: PFS (a) and OS (b). CONUT, controlling nutritional status.

Stage III

Stage IV

Figure 3

Kaplan-Meier survival analyses of PFS (a) and OS (b), according to CONUT, among patients in the stage III and stage IV subgroups. CONUT, controlling nutritional status.